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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Wetzel *et al.*		
ASSIGNEE:	CELL SIGNALING TECHNOLOGY, INC.		
SERIAL NUMBER:	10/807,799	EXAMINER:	Not yet assigned
FILING DATE:	March 24, 2004	ART UNIT:	1645
FOR:	ANTIBODIES SPECIFIC FOR BCR-ABL FUSION PROTEIN AND USES THEREOF		

June 14, 2005
Beverly, Massachusetts

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Pursuant to the duty of disclosure under 37 C.F.R. §§1.56, 1.97 and 1.98, Applicants hereby make of record the documents listed below and on the attached modified Form PTO-1449 (submitted in duplicate) in the above-identified application. The order of presentation of the references should not be construed as an indication of the importance of the references.

U.S. Patent or Application Documents:

6,686,165	van Dongen *et al.*	February 3, 2004

Foreign Patent Documents:

Other Prior Art – Non Patent Literature Documents:

Name of Author, Title (when appropriate), Publication, Volume, Page(s), Date, Etc.
van Denderen *et al., Leukemia,* Vol. 6(11): 1107-1112 (November 1992)
van Denderen *et al., J. Exp. Med.,* Vol. 169: 187-98 (January 1989)
van Denderen *et al., Leuk. Lymph.*, Vol. 11(Supp. 1): 29-32 (1993)

This Information Disclosure Statement is being filed:

☐ within three months of the filing date of the National Application;

☐ within three months of the filing date of the entry of the National Stage, as set forth in 37 C.F.R. §1.491, in an International Application; or

☒ before the mailing date of a first Office Action on the merits in the above-identified case.

Accordingly, no fee or certification is required. 37 C.F.R. §1.97.

This Information Disclosure Statement is being filed:

☐ after the mailing of a first Office Action on the merits, but before the mailing date of a final Office Action, a Notice of Allowance, or an action that otherwise closes prosecution in the application; and

☐ is accompanied by the following statement:

☐ Applicant(s) hereby state(s) that each item of information contained in this information disclosure statement was first cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement (37 C.F.R §1.97(e)(1)); or

☐ Applicant(s) hereby state(s) that no item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned representative signing this certification after making reasonable inquiry, no item of information contained in this information disclosure statement was known to any individual designated in Rule 1.56(c) more than three months prior to the filing of this information disclosure (37 C.F.R §1.97(e)(2)); and

☐ is accompanied by the fee set forth in 37 C.F.R. §1.17(p):

☐ a check for the required fee is enclosed herewith; or

☐ the Commissioner is hereby authorized to charge the required fee (and any other fees that may be due) to U.S. Deposit Account No. 50-1774, Ref. No. CST-_____.

A copy of each of the above-identified information is enclosed unless otherwise indicated on the attached Form PTO-1449 (modified). It is respectfully requested that the Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims, and signs the enclosed form PTO-1449 to evidence that the cited information has been fully considered by the Patent and Trademark Office during the examination of this application.

REMARKS

Submitted herewith for the Examiner's consideration are three papers, van Denderen *et al.* (1992) (Ref. CR), van Denderen *et al.* (1989) (Ref. CS), and van Denderen *et al.* (1993) (Ref. CT), which describe early, but unsuccessful, attempts to produce Bcr-Abl fusion protein specific antibodies. The polyclonal antisera described in these papers are readily distinguished from the presently claimed subject matter in several important ways. Most notably, none of the references discloses an isolated antibody that specifically binds a p210 Bcr-Abl fusion protein *but does not bind* wild type Bcr and wild type Abl proteins. Since the p210 Bcr-Abl fusion protein is characteristic of Chronic Myelogenous Leukemia (CML), antibodies that cross-react with wild type Bcr and Abl proteins are not useful in the diagnosis of this important disease. As noted in the Background of the instant specification, this undesirable cross-reactivity is the problem solved by the antibodies of the invention.

The present invention provides an isolated antibody that specifically binds the human p210 Bcr-Abl fusion protein (b2-a2 chimer) *but does not bind* wild type Bcr or Abl. The invention solves a long-felt but previously unmet need in the art for an antibody truly specific for the p210 Bcr-Abl fusion protein that is the hallmark of CML. The antibody provided by the invention was raised against the following peptide corresponding to the b2-a2 fusion joint in human p210 Bcr-Abl, *LTINKE*<u>E</u>**ALQRPVAS** (where the underlined glutamic acid is newly created in the fusion, the italicized residues correspond to wild type Bcr protein, and the bold residues correspond to wild type Abl protein). The antibody was specifically tested for, and shown to have, lack of cross-reactivity to either wild type Bcr or wild type Abl. The antibody provided by the invention was also tested for, and established as, being suitable for use in Western Blot assay, as well as cell-based assays such as flow cytometry (FC) and immunohistochemistry (IHC), which are desirably employed in diagnostic/clinical settings.

In contrast, Ref. CR describes the production of a polyclonal antiserum (BP-2), to a different chimer of Bcr-Abl (the b3-a2 fusion) that is not truly fusion-protein specific. The paper describes BP-2 as being raised against a peptide corresponding to the b3-a2 fusion joint in Bcr-Abl, which has the following splice junction sequence, *GFKQSS*<u>K</u>**ALQ** (where the underlined lysine is newly created in the fusion, the italicized residues correspond to wild type Bcr protein, and the bold residues correspond to wild type Abl protein). Although the BP-2 antiserum was

tested in immuno-precipitation experiments for specificity against native Bcr-Abl and shown to bind the b3-a2 chimer (but not the b2-a2 chimer) as expected, the antiserum was *not* tested against wild type Bcr and wild type Abl to establish that it did not cross react with these proteins.[1] Indeed, the BP-2 antiserum was disclosed to undesirably cross-react with the b3 portion of the fusion peptide, and the authors expressly concluded that it was *not suitable* for detecting only the Bcr-Abl fusion protein in cellular experiments because it would also bind wild type Bcr (*see* p. 1111, left column, last paragraph). Accordingly, the BP-2 antiserum disclosed in Ref. CR does not have the specificity, lack of cross-reactivity, or suitability for cell-based assay formats that the antibody of the invention possesses.

Ref. CS (by the same authors) similarly describes the production of a polyclonal antiserum (BP-1) to the b2-a2 chimer of Bcr-Abl fusion protein that is not truly fusion-protein specific. The paper describes BP-1 as being raised against a peptide corresponding to the b2-a2 fusion joint in Bcr-Abl, which has the following splice junction sequence, *INKE*E**ALQRP** (where the underlined glutamic acid is newly created in the fusion, the italicized residues correspond to wild type Bcr protein, and the bold residues correspond to wild type Abl protein). The BP-1 antiserum was tested and shown to undesirably cross-react with the b3-a2 fusion peptide, which the authors concluded was likely due to the shared a2 portion of the fusion joint peptide (*see* p. 90, first paragraph). The authors also tested the BP-1 antiserum, in immunoprecipitation experiments, to establish that it binds the native b2-a2 Bcr-Abl chimer (but not the b3-a2 chimer), somewhat surprising given the cross-reactivity observed in peptide inhibition experiments. However, the antiserum was *not* tested against wild type Bcr and wild type Abl to establish that it did not cross react with these proteins.[2] Accordingly, the BP-1 antiserum disclosed in Ref. CS does not have the specificity, lack of cross-reactivity, or suitability for cell-based assay formats that the antibody of the invention possesses.

Ref. CT (by the same authors) similarly describes the detection of BCR-ABL fusion

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[1] In fact, Figure 3 of Ref. CR, which is blot of immunoprecipitated K562 cell extracts, appears to indicate that antiserum BP-2 undesirably binds wild type Abl, which is consistent with the fact that this cell line is known to express wild type Abl in addition to the p210 Bcr-Abl fusion protein.

[2] In fact, the authors expressly conclude, following absorption studies with BP-1, that the majority of the antibodies in this antiserum bind the b2 side of the b2-a2 fusion joint, which implies that this antiserum will, in fact, undesirably cross-react with wild type Bcr (*see* end of p. 91 to top of p. 92).

proteins in leukemic cell lines using the BP-1 and BP-2 antisera earlier described. This reference suffers from the same limitations as Refs. CR and CS above. Indeed, the authors expressly conclude by stating that the disclosed antisera are not specific in, nor suitable for, immunofluorescence assays, a common diagnostic cell-based format (see p. 32, last paragraph).

The failure of prior art attempts, such as those described in Refs. CR, CS, and CT, to produce a truly useful p210 Brc-Abl fusion protein-specific antibody lacking undesirable cross-reactivity with wild type Brc and Abl has been poignantly underscored in several publications. Most notably, the authors of Refs. CR, CS, and CT themselves, in later U.S. patents directed to improved methods of detecting Bcr-Abl fusion proteins, state that "Immunological detection of the fusion proteins resulting from chromosomal aberrations has, although widely tried, never been successful . . . Usually, such antibodies cross-react with normal cellular proteins . . ." (*see* U.S. Patent No. 6,686,165, van Dongen *et al.*, February 2, 2004 (Ref. AC) and U.S. Patent No. 6, 610,498, Berendes *et al.*, August 26, 2003 (Ref. AA) (previously submitted), both at Background, 2nd to last paragraph). Another review article, Falini *et al.*, *Blood 99(2): 409-426* (Ref. CQ) (previously submitted and cited in the Background of the instant application), discusses methods for clinically detecting cancer fusion proteins like Brc-Abl. This paper specifically cites Refs. CR and CS and states that the antibodies described in those papers (and others) are *not* useful for cell-based fusion protein detection, and further states that "although in theory it should be possible to produce antibodies specific for hybrid proteins, in practice such antibodies remain elusive . . . Antibodies specific for chimeric oncogene products will therefore always be difficult, if not impossible, to produce . . ." (*see* Ref. CQ at p. 420, left column).

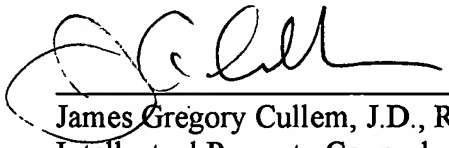
In summary, the human p210 Brc-Abl fusion protein specific antibody provided by the present invention is a novel, surprising, and important advance over prior antibodies, and will enable new diagnostic methods for CML that were previously not possible due to undesirable cross-reactivity with wild type Brc and Abl proteins.

By submitting this Information Disclosure Statement, the Applicant makes no representation that: (1) a search has been performed, of the extent of any search performed, or that more relevant information does not exist; (2) the information cited in the Statement is, or is

considered to be, material to patentability as defined in 37 C.F.R. §1.56(b); and (3) the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. §102.

Notwithstanding any statements by the Applicant, the Examiner is urged to form his/her own conclusion regarding the relevance of the cited information. Early and favorable allowance of the present application is hereby requested. Please charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-1774, Reference No. CST-214.

Respectfully submitted,



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ASSIGNEE:	Cell Signaling Technology, Inc.		
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Alexandria, VA 22313-1450

Attached hereto for filing in the above-identified patent application are the following:

- ☒ Transmittal Letter (w/duplicate) (2 pages);
- ☒ Supplemental Information Disclosure Statement (6 pages);
- ☒ Form 1440/PTO Information Disclosure Statement w/duplicate (2 pages);
- ☒ References AC, CR, CS and CT (4 references);
- ☒ Return Postcard.

Respectfully submitted,

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Modified Form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Application Number	10/807,799
Filing Date	March 24, 2004
First Named Inventor	Wetzel *et al.*
Group Art Unit	1645
Examiner Name	Not yet assigned
Attorney Docket Number	CST-214

U.S. PATENT DOCUMENTS

Exam Initials	Cite No.	U.S. Patent Document No.	Issue Date	Name of Patentee(s) or Applicant(s)	Class	Sub Class	Filing Date If Appropriate
	AC	6,686,165	02/03/2004	*van Dongen, et al*			

FOREIGN PATENT DOCUMENTS

Exam Initials	Cite No.	Foreign Patent Document Office	Number	Name of Patentee(s) or Applicant(s)	Date of Publication	Translation Yes	No

OTHER NON PATENT LITERATURE DOCUMENTS

Exam Initials	Cite No.	Name of Author, Title (when appropriate), Publication, Volume, Page(s), Date, Etc.
	CR	van Denderen, *et al., LEUKEMIA,* Vol 6, 11: 1107-1112 (November 1992)
	CS	van Denderen *et al., J. Exp. Med.,* Volume 169: 187-98 (January 1989)
	CT	van Denderen, *et al., Leuk. Lymph.,* Vol. 11 (Supp. 1): 29-32 (1993)

* a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, U.S.S.N. _____ , filed _____ , and relied upon for an earlier filing date under 35 U.S.C. §120 (continuation, continuation-in-part, and divisional applications).

Examiner Signature		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered.

Include copy of this form with next communication to applicant.